Interactions of dietary fat intake and the hepatic lipase -480C->T polymorphism in determining hepatic lipase activity: the Hoorn Study

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Interactions of dietary fat intake and the hepatic lipase −480C→T polymorphism in determining hepatic lipase activity: the Hoorn Study[1–3]

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ABSTRACT

Background: Gene-nutrient interactions affecting hepatic lipase (HL) activity may contribute to the interindividual variability of the cardiovascular disease risk associated with dietary fat intake.

Objective: We determined the associations of dietary fat intake with postheparin HL activity and the possible modifying effect of the HL −480C→T polymorphism on these associations.

Design: Subjects were recruited from participants in the 2000–2001 follow-up examination of the Hoorn Study. HL activity was determined in postheparin plasma in a sample of 211 men and 218 women aged 60–87 y. Information about dietary intake of the participants was obtained with a validated food-frequency questionnaire. Linear regression was performed, adjusted for age.

Results: Total dietary fat was positively associated with HL activity (standardized β: 0.11; 95% CI: 0.02, 0.21), and this association was also seen for saturated fat (0.10; 0.01, 0.20) and monounsaturated fatty acid (0.10; 0.01, 0.19). We observed a significant interaction of the HL polymorphism with the relation between total fat intake and HL activity. The association of total fat with HL activity was stronger in subjects with *CT* (0.27; 0.11, 0.43) and *TT* (0.39; −0.22, 1.00) genotypes than in subjects with the *CC* genotype (0.06; −0.06, 0.18; P for interaction < 0.10). The interaction remained statistically significant in models that included age, sex, carbohydrate and protein intakes, and insulin or body mass index.

Conclusions: Higher intakes of total and saturated fat were positively associated with higher HL activity. In addition, the observed association of total fat with HL activity was modified by the HL−480C→T polymorphism, after adjustment for age, sex, carbohydrate and protein intakes, and insulin or body mass index. *Am J Clin Nutr* 2005;81:911–5.

KEY WORDS Hepatic lipase, gene-nutrient interaction, fat intake

INTRODUCTION

Dietary fat intake is an important predictor of serum lipids and lipoproteins (1–3). Reduction in saturated fat intake is associated with decreases in plasma LDL-cholesterol and HDL-cholesterol concentrations. Triacylglycerol and phospholipids in HDL and LDL particles are hydrolyzed by hepatic lipase (HL), a lipolytic enzyme, resulting in the formation of smaller and denser particles.

HL activity has been shown to be determined by genetic factors (4). A common −480C→T substitution, also denominated LIPC −514C→T (5), has been described in the promoter region of the HL gene (6). The *T* allele is associated with decreased plasma HL activity (6, 7). Dietary fat has recently been shown to modify the association between HL −480C→T polymorphism and plasma HDL-cholesterol concentrations in such a way that the presence of the *T* allele was associated with higher HDL cholesterol, only in individuals who usually consume a low-fat diet. In contrast, the *TT* genotype was associated with lower HDL cholesterol in individuals who usually consume a high-fat diet (8). Information about the effects of dietary fat on HL activity is limited and contradictory. A high-fat diet (46% of energy) increased HL activity in 43 healthy men compared with a low-fat diet (24% of energy) (9). However, no differences in HL activity were observed after dietary fat restriction in 72 healthy women (10). In an intervention study with low-fat and high-fat diets in men, an increase in dietary saturated fat was associated with decreased HL activity (11).

In this cross-sectional observational study of 429 men and women, we investigated the association of both dietary fat intake and HL −480C→T polymorphism with HL activity. In addition, we determined whether the HL −480C→T polymorphism modifies the association of dietary fat intake with plasma postheparin HL activity.

SUBJECTS AND METHODS

Design and population

The Hoorn Study is a population-based cohort study of glucose metabolism and cardiovascular disease risk factors among the inhabitants of the municipality of Hoorn, Netherlands, which started in 1989 and consisted of 2484 subjects, as described

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before (12). In 2000–2001, a follow-up was conducted in selected subjects, then aged 60–87 y. We invited all surviving subjects with type 2 diabetes ($n = 176$) to participate and also individuals chosen from random samples with normal glucose metabolism ($n = 705$) or impaired glucose metabolism ($n = 193$) on the basis of their glucose metabolism status at the previous examination in 1996–1998 (13). Of the 1074 individuals invited, 648 (60.3%) participated in the 2000–2001 follow-up examination. Among the reasons for not participating in the follow-up examinations were lack of interest (30%), comorbidity (23%), advanced age (7%), unwillingness to travel (6%), participation considered too time consuming (6%), and miscellaneous reasons (15%). Thirteen percent were complete nonresponders. For the present study, cross-sectional data of this 2000–2001 follow-up examination were analyzed. A sample of 585 participants was invited for the postheparin test, of which 566 participated. The Ethical Review Committee of the VU University Medical Center approved the study. Informed consent was obtained from all participants.

Postheparin plasma HL activity

HL activity was measured by using an immunochemical method as described previously in plasma collected 20 min after contralateral intravenous administration of 50 IU heparin/kg body weight (Leo Pharmaceutical Products, Weesp, Netherlands). One hundred seven samples (19%) were excluded from the analysis because of low activities for lipoprotein lipase (LPL) and HL in postheparin plasma. The cutoffs for low lipase activities were selected on the basis of visual inspection of a scatterplot. Activities were considered low if both LPL activity was <50 U/L and HL activity was <72 U/L. Inclusion of other subjects with incomplete heparin injections did not change the results (data not shown). Most excluded samples were among subjects with impaired glucose metabolism and type 2 diabetes. However, no statistically significant differences were observed between individuals who were excluded and the rest of the subjects with respect to lipoproteins, body mass index (BMI), and dietary fat intake (data not shown). Furthermore, HL activity showed the known associations with age, sex, HDL-cholesterol concentration, and triacylglycerol concentration (4, 14). The postheparin test was repeated in a sample of subjects with normal and impaired glucose metabolism and diabetes with both low LPL and HL activities ($n = 10$). Normal LPL and HL activities were measured in these subjects, indicating that insufficient heparin delivery was the cause of the low activities.

Genotyping HL polymorphism

DNA was extracted from blood. We used the polymerase chain reaction method as described by Berk-Planken et al (15) to assess the presence of the *C>T* variance in the HL gene promoter.

Glycemic control and lipids

All participants underwent a 75-g oral-glucose-tolerance test, except for participants with capillary fasting whole blood glucose concentrations ≥8 mmol/L or participants with a previous diagnosis of diabetes who were treated with oral glucose-lowering medication or insulin. Fasting glucose and 2-h postload glucose were measured in plasma with the hexokinase method (Roche Diagnostics GmbH, Mannheim, Germany). Glycated hemoglobin was analyzed by HPLC (reference range: 4.3–6.1%). Fasting plasma glucose, 2-h postload plasma glucose, total-cholesterol, HDL-cholesterol, and triacylglycerol concentrations were measured by enzymatic methods (Roche, Mannheim, Germany). LDL cholesterol was directly determined by the N-geneous assay (Genzyme, Cambridge, MA). Insulin was determined by using a two-site immunoradiometric test. Paired monoclonal antibodies were used (Medgenix, Diagnostics, Fleurus, Belgium).

Dietary intake

Information about the dietary intake of the participants was obtained by a validated food-frequency questionnaire (16, 17), which was linked to an extended version of the computerized Dutch Food Composition Table 1996 (18). Intake of macronutrients was expressed as the percentage of energy as fat [fat (in kJ)/total energy (in kJ) × 100].

Statistical analysis

Three glucose metabolism categories (normal, impaired glucose metabolism, and diabetes) were defined according to the World Health Organization criteria (19). We excluded people with missing data on primary variables of interest (glucose metabolism, $n = 7$; HL activity, $n = 107$; HL −480C→T polymorphism, $n = 17$; and dietary intake, $n = 6$). Thus, the study population consisted of 429 individuals, 211 men and 218 women. Characteristics of the study population are presented by polymorphism category. To depict the independent associations of dietary fat with HL activity, the population was divided into 9 groups by creating a 3 × 3 table according to tertiles of fat intake and HL polymorphism groups. To investigate the association of dietary fat intake (percentage of energy) to the HL activity, linear regression analysis was performed. HL activity was modeled as the dependent variable and dietary fat intake as independent variable. The coefficients for the individual types of fat were obtained by putting each fat in an individual model. All regression models were adjusted *1*) for age; additionally *2*) for sex, consumption of carbohydrates, and consumption of proteins; and *3*) for insulin concentration and glucose metabolism status or BMI. Stratified analyses were performed to evaluate possible effect modification by polymorphism. If we observed a linear trend in the standardized $\bar{a}$ coefficients, we tested for interactions of HL polymorphism by calculating the respective interaction terms. With an *F* test we checked whether these product terms significantly improved the model. All associations of the regression analyses are reported as standardized β coefficients. A standardized β of −0.1 indicates that, if the independent variable increases 1 SD, the dependent variable (HL activity) decreases 0.1 SD. *P* values < 0.05 were considered statistically significant, except for interaction analyses, in where we used $P < 0.10$. Statistical analyses were performed with SPSS for WINDOWS version 10.1 (SPSS Inc, Chicago).

RESULTS

HL activity was significantly lower in carriers of the *TT* genotype than in subjects with the *CC* or *CT* genotype (*P* for trend < 0.001; **Table 1**). Furthermore, the carriers of the *TT* genotype had a more favorable lipid profile, ie, with higher HDL cholesterol (*P* for trend = 0.03). The SD for fasting glucose in

TABLE 1
Baseline characteristics of the population according to hepatic lipase −480C→T polymorphism[1]

	HL polymorphism			
	CC (n = 275)	*CT* (n = 142)	*TT* (n = 12)	*P* for trend
Age (y)	70 ± 6[2]	69 ± 6	71 ± 9	0.95
Sex (% male)	50	47	50	0.64
Hepatic lipase (U/L)	385 ± 132	357 ± 134	242 ± 53	<0.001
Fasting glucose (mmol/L)	6.09 ± 1.32	6.14 ± 1.20	7.08 ± 3.64	0.80
Postload glucose (mmol/L)	6.93 ± 2.27	7.08 ± 2.77	6.54 ± 1.29	0.73
Insulin (pmol/L)	53 (39–75)[3]	57 (39–84)	42 (32–80)	0.75
Total cholesterol (mmol/L)	5.7 ± 1.1	5.8 ± 0.9	5.7 ± 1.0	0.28
HDL cholesterol (mmol/L)	1.40 ± 0.40	1.48 ± 0.44	1.55 ± 0.35	0.03
LDL cholesterol (mmol/L)	3.7 ± 0.9	3.7 ± 0.9	3.7 ± 0.8	0.77
Triacylglycerol (mmol/L)	1.3 (1.0–1.7)	1.3 (0.9–1.7)	1.1 (0.9–1.4)	0.87
Systolic blood pressure (mm Hg)	142 ± 20	141 ± 22	139 ± 19	0.52
Diastolic blood pressure (mm Hg)	82 ± 11	82 ± 11	82 ± 14	0.69
Antihypertensive drugs (%)	67	64	83	0.07
Lipid lowering (%)	16	13	0	0.21
BMI (kg/m^2)	26.7 ± 3.4	27.3 ± 4.2	26.3 ± 3.1	0.15
Energy intake (kJ/d)	8296 ± 3584	8367 ± 2197	7364 ± 1959	0.89
Total fat intake (% of energy)	34.5 ± 5.9	34.4 ± 5.8	37.8 ± 4.3	0.20
Saturated fat intake (% of energy)	14.7 ± 3.2	14.4 ± 2.6	17.2 ± 3.3	0.28
MUFA intake (% of energy)	13.1 ± 2.6	13.0 ± 2.8	14.0 ± 2.2	0.21
PUFA intake (% of energy)	6.4 ± 2.2	6.6 ± 2.4	6.1 ± 1.9	0.71
Carbohydrate (% of energy)	45.7 ± 7.1	45.8 ± 6.2	43.4 ± 5.9	0.69
Protein (% of energy)	15.2 ± 2.5	15.2 ± 2.3	15.4 ± 2.4	0.69

[1] MUFA, monounsaturated fat; PUFA, polyunsaturated fat.
[2] $\bar{x}$ ± SD (all such values).
[3] Median; interquartile range in parentheses (all such values).

the *TT* group is large, because there was one outlier with a fasting glucose concentration of 18.5 mmol/L. Nevertheless, we did not exclude this subject from the analysis; the extreme value was a true observation because the person was a diabetic subject. No significant differences in dietary fat intake across HL polymorphisms were detected. Genotype frequencies did not deviate from the Hardy-Weinberg equilibrium.

The HL −480C→T polymorphism was the strongest predictor of HL activity [β (95% CI): −28 (−54, −4) for the *CT* and −138 (−210; −66) for the *TT* genotypes compared with the *CC* genotype]. Intakes of total fat, saturated fat, and monounsaturated fat were positively associated with HL activity, whereas intake of polyunsaturated fatty acid was not related to HL activity (**Table 2**). A test for interaction between total fat and HL polymorphism was significant ($P < 0.10$), indicating that the association of total dietary fat intake with HL activity differs across categories of HL −480C→T polymorphism.

In **Table 3**, stratified multivariate analyses of total fat intake and HL activity are shown. After adjustment for carbohydrate intake, protein intake, and insulin concentration (model 2), total

TABLE 2
Standardized β coefficients (95% CIs) for age-adjusted associations of dietary fat intake with hepatic lipase (HL) activity by HL −480C→T polymorphism: univariate regression analyses[1]

	HL polymorphism			
	CC (n = 275)	*CT* (n = 142)	*TT* (n = 12)	Overall (n = 429)
Total fat	0.06 (−0.06, 0.18)	0.27 (0.11, 0.43)[2]	0.39 (−0.22, 1.00)	0.11[3] (0.02, 0.21)[4]
Saturated fat	0.11 (−0.01, 0.23)	0.17 (0.01, 0.33)	0.24 (−0.20, 0.41)	0.10 (0.01, 0.20)
MUFA	0.04 (−0.07, 0.16)	0.23 (0.07, 0.39)	0.43 (−0.15, 1.01)	0.10 (0.01, 0.19)
PUFA	−0.05 (−0.17, 0.07)	0.20 (0.04, 0.36)	−0.03 (−0.71, 0.66)	0.04 (−0.06, 0.13)

[1] MUFA, monounsaturated fat; PUFA, polyunsaturated fat.
[2] Significant association of total fat intake with HL activity in the model, $P < 0.05$.
[3] A standardized β of 0.11 indicates that if the independent variable (total fat intake) increases by 1 SD, the dependent variable (HL activity) will increase by 0.11 SD. This corresponds with a slope (β) of 2.61, which indicates that if the total fat intake increases by 1% of energy, HL activity will increase by a mean of 2.61 U/L in the entire population. The reason that we used standardized β coefficients was because of the possibility of making comparisons between different models, ie, the association between different types of fat and HL activity.
[4] Simultaneous test for both interaction terms, $P = 0.09$.

TABLE 3
Standardized β coefficients (95% CI) for associations of dietary total fat intake with hepatic lipase (HL) activity by HL −480C→T polymorphism: multivariate regression analysis

	HL polymorphism			
Model[1]	*CC* (n = 275)	*CT* (n = 142)	*TT* (n = 12)	P for interaction[2]
1	−0.02 (−0.17, 0.12)	0.19 (−0.02, 0.40)	0.35 (−1.24, 1.93)	0.13
2	−0.04 (−0.19, 0.10)	0.20 (−0.002, 0.41)	0.25 (−1.02, 1.52)	0.07
3	−0.03 (−0.17, 0.11)	0.22 (0.02, 0.42)	0.50 (−0.97, 1.97)	0.11
4	−0.05 (−0.19, 0.08)	0.23 (0.03, 0.43)[3]	0.29 (−0.81, 1.38)	0.04

[1] Model 1, total fat intake adjusted for age, sex, and carbohydrate and protein intakes; model 2, model 1 + insulin; model 3, model 1 + glucose metabolism status; model 4, model 1 + BMI.
[2] Interaction between total fat intake and HL polymorphism.
[3] Significant association of total fat intake with HL activity in the model, $P < 0.05$.

fat intake tended to be positively associated with HL activity in subjects with *CT* and *TT* genotypes, but not in subjects with the *CC* genotype; however, none of these associations was statistically significant. These associations were seen after additional adjustment for insulin and not after adjustment for carbohydrate and protein intake only (model 1). After adjustment for glucose metabolism status or BMI (models 3 and 4), a positive association was observed between total fat intake and HL activity in the same direction as in models 1 and 2. These associations were statistically significant for the *CT* genotype in model 3. The overall *F* test for interactions between total fat and HL polymorphisms reached statistical significance after adjustment for carbohydrate and protein intakes, insulin ($P = 0.07$; model 2), and BMI ($P = 0.04$; model 4).

DISCUSSION

In this population-based study, we describe the effects of dietary fat intake on HL activity. We found that the *T* allele was associated with lower HL activity, and this relation was independent of the amount and type of fat consumed. In addition, we found a stronger association of total dietary fat intake with HL activity in subjects with *CT* and *TT* genotypes than in subjects with the *CC* genotype, after adjustment for age, sex, carbohydrate and protein intakes, and insulin or BMI.

In the Framingham study, the *T* allele was associated with significantly greater HDL-cholesterol concentrations only in subjects consuming <30% of energy from fat (8). The observed gene-nutrient interaction with HDL cholesterol was in the same direction as our findings with HL activity. In line with our results, higher intake of saturated fat was associated with higher HL activity in 43 men in a study of Dreon et al (11). It has been described that HL activity is quite variable, indicating that other factors affect HL activity. HL activity is higher in men, in smokers, and in those with diabetes, and it is positively associated with intraabdominal fat and BMI (4, 14). Thus, HL activity is associated with several components of the insulin resistance syndrome (15, 20–23).

The design of our study did not allow us to investigate the mechanism by which dietary fat possibly interacts with the −480C→T polymorphism. Investigations in rats have shown that the dietary lipid profile is an important predictor of tissue phospholipid composition (24), which may, in turn, influence insulin sensitivity by altering membrane fluidity and insulin signaling (25, 26). One possibility is a direct effect of fatty acids on HL expression. It has been shown that fatty acids enhance HL activity secreted from HepG2 cells (27). Therefore, HL activity could be modulated by a change in the supply of fatty acids to the liver either from the diet or from the omental fat stores. Additionally, it has been hypothesized that the underlying mechanism could be insulin resistance of the *T* allele at the level of gene expression (H Jansen, unpublished observations, 2004). Previous studies have reported that insulin up-regulates the activity of HL by insulin-responsive elements in the HL promoter, suggesting that variants in this promoter, as examined in this study, may affect the ability of insulin to stimulate HL activity (28). Jansen et al (6) have reported an association between variants of the HL promoter and insulin resistance. However, in our study, adjustment for insulin concentration did not change the observed association between total fat intake and HL activity in any of the genotypes.

Some limitations of our study should be noted. First, the number of subjects in the groups with the *TT* genotype was small (n = 12), thus reducing the statistical power for conclusions about this group. However, this study is the first to measure HL activity in such a large population and to investigate relations between HL activity and HL polymorphisms. Furthermore, we observed different associations in the *CT* genotype group. Second, our findings were obtained in the elderly. Therefore, we may have underestimated the association of dietary fat intake with HL activity because of selective morbidity and mortality of individuals with unhealthy lifestyle and food consumption and consequently unfavorable lipase activity or related lipoproteins.

In summary, total dietary fat and saturated fat were positively associated with HL activity. In addition, we observed a gene-nutrient interaction (in a model that included BMI), such that the association of the amount of total fat consumed with HL activity depended on the HL −480C→T polymorphism. Gene-nutrient interactions may help to explain the different outcomes of plasma lipoprotein in response to dietary fat and the conflicting results about HL activity and cardiovascular disease risk.

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GB performed the data analyses and wrote the drafts and final paper. JMD, MCO, EJMF, GN, CDAS, LMB, RJH, and HJ provided advice concerning

the presentation and interpretation of the results. JMD, EJMF, and HJ participated in the conception of the study. JMD, LMB, CDAS, RJH, and GN designed and collected data for the Hoorn Study. MCO provided the nutritional data. None of the authors had a conflict of interest.

REFERENCES

1. Mensink RP, Zock PL, Kester AD, Katan MB. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. Am J Clin Nutr 2003;77:1146–55.
2. Mensink RP, Katan MB. Effect of dietary fatty acids on serum lipids and lipoproteins. A meta-analysis of 27 trials. Arterioscler Thromb 1992;12:911–9.
3. Hegsted DM, Ausman LM, Johnson JA, Dallal GE. Dietary fat and serum lipids: an evaluation of the experimental data. Am J Clin Nutr 1993;57:875–83.
4. Tan KC, Shiu SW, Chu BY. Effects of gender, hepatic lipase gene polymorphism and type 2 diabetes mellitus on hepatic lipase activity in Chinese. Atherosclerosis 2001;157:233–9.
5. Guerra R, Wang J, Grundy SM, Cohen JC. A hepatic lipase (LIPC) allele associated with high plasma concentrations of high density lipoprotein cholesterol. Proc Natl Acad Sci U S A 1997;94:4532–7.
6. Jansen H, Verhoeven AJ, Weeks L, et al. Common C-to-T substitution at position −480 of the hepatic lipase promoter associated with a lowered lipase activity in coronary artery disease patients. Arterioscler Thromb Vasc Biol 1997;17:2837–42.
7. Deeb SS, Zambon A, Carr MC, Ayyobi AF, Brunzell JD. Hepatic lipase and dyslipidemia: interactions between genetic variants, obesity, gender and diet. J Lipid Res 2003;44:1279–86.
8. Ordovas JM, Corella D, Demissie S, et al. Dietary fat intake determines the effect of a common polymorphism in the hepatic lipase gene promoter on high-density lipoprotein metabolism: evidence of a strong dose effect in this gene-nutrient interaction in the Framingham Study. Circulation 2002;106:2315–21.
9. Campos H, Dreon DM, Krauss RM. Associations of hepatic and lipoprotein lipase activities with changes in dietary composition and low density lipoprotein subclasses. J Lipid Res 1995;36:462–72.
10. Kasim SE, Martino S, Kim PN, et al. Dietary and anthropometric determinants of plasma lipoproteins during a long-term low-fat diet in healthy women. Am J Clin Nutr 1993;57:146–53.
11. Dreon DM, Fernstrom HA, Campos H, Blanche P, Williams PT, Krauss RM. Change in dietary saturated fat intake is correlated with change in mass of large low-density-lipoprotein particles in men. Am J Clin Nutr 1998;67:828–36.
12. Mooy JM, Grootenhuis PA, de Vries H, et al. Prevalence and determinants of glucose intolerance in a Dutch caucasian population. The Hoorn Study. Diabetes Care 1995;18:1270–3.
13. de Vegt F, Dekker JM, Jager A, et al. Relation of impaired fasting and postload glucose with incident type 2 diabetes in a Dutch population: the Hoorn Study. JAMA 2001;285:2109–13.
14. Kong C, Nimmo L, Elatrozy T, et al. Smoking is associated with increased hepatic lipase activity, insulin resistance, dyslipidaemia and early atherosclerosis in type 2 diabetes. Atherosclerosis 2001;156:373–8.
15. Berk-Planken II, Hoogerbrugge N, Stolk RP, Bootsma AH, Jansen H. Atorvastatin dose-dependently decreases hepatic lipase activity in type 2 diabetes: effect of sex and the LIPC promoter variant. Diabetes Care 2003;26:427–32.
16. Ocke MC, Bueno-de-Mesquita HB, Pols MA, Smit HA, van Staveren WA, Kromhout D. The Dutch EPIC food frequency questionnaire. II. Relative validity and reproducibility for nutrients. Int J Epidemiol 1997;26(suppl):S49–58.
17. Ocke MC, Bueno-de-Mesquita HB, Goddijn HE, et al. The Dutch EPIC food frequency questionnaire. I. Description of the questionnaire, and relative validity and reproducibility for food groups. Int J Epidemiol 1997;26(suppl):S37–48.
18. Stichting NEVO. NEVO tabel. Nederlands Voedingsstoffenbestand 1996. (NEVO table. Dutch nutrient database 1996.) Den Haag: Voorlichtingsbureau voor de Voeding, 1996 (in Dutch).
19. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. Diabet Med 1998;15:539–53.
20. Tan KC, Shiu SW, Chu BY. Roles of hepatic lipase and cholesteryl ester transfer protein in determining low density lipoprotein subfraction distribution in Chinese patients with non-insulin-dependent diabetes mellitus. Atherosclerosis 1999;145:273–8.
21. Frenais R, Nazih H, Ouguerram K, et al. In vivo evidence for the role of lipoprotein lipase activity in the regulation of apolipoprotein AI metabolism: a kinetic study in control subjects and patients with type II diabetes mellitus. J Clin Endocrinol Metab 2001;86:1962–7.
22. Tan KC, Cooper MB, Ling KL, et al. Fasting and postprandial determinants for the occurrence of small dense LDL species in non-insulin-dependent diabetic patients with and without hypertriglyceridaemia: the involvement of insulin, insulin precursor species and insulin resistance. Atherosclerosis 1995;113:273–87.
23. Riemens SC, Van Tol A, Stulp BK, Dullaart RP. Influence of insulin sensitivity and the TaqIB cholesteryl ester transfer protein gene polymorphism on plasma lecithin:cholesterol acyltransferase and lipid transfer protein activities and their response to hyperinsulinemia in nondiabetic men. J Lipid Res 1999;40:1467–74.
24. Pan DA, Storlien LH. Dietary lipid profile is a determinant of tissue phospholipid fatty acid composition and rate of weight gain in rats. J Nutr 1993;123:512–9.
25. Feskens EJ, Loeber JG, Kromhout D. Diet and physical activity as determinants of hyperinsulinemia: the Zutphen Elderly Study. Am J Epidemiol 1994;140:350–60.
26. Marshall JA, Bessesen DH, Hamman RF. High saturated fat and low starch and fibre are associated with hyperinsulinaemia in a non-diabetic population: the San Luis Valley Diabetes Study. Diabetologia 1997;40:430–8.
27. Nimmo L, McColl AJ, Rosankiewicz JZ, Richmond W, Elkeles RS. Regulation of hepatic lipase expression in HepG2 cells. Biochem Soc Trans 1997;25:S689.
28. Thuren T. Hepatic lipase and HDL metabolism. Curr Opin Lipidol 2000;11:277–83.

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